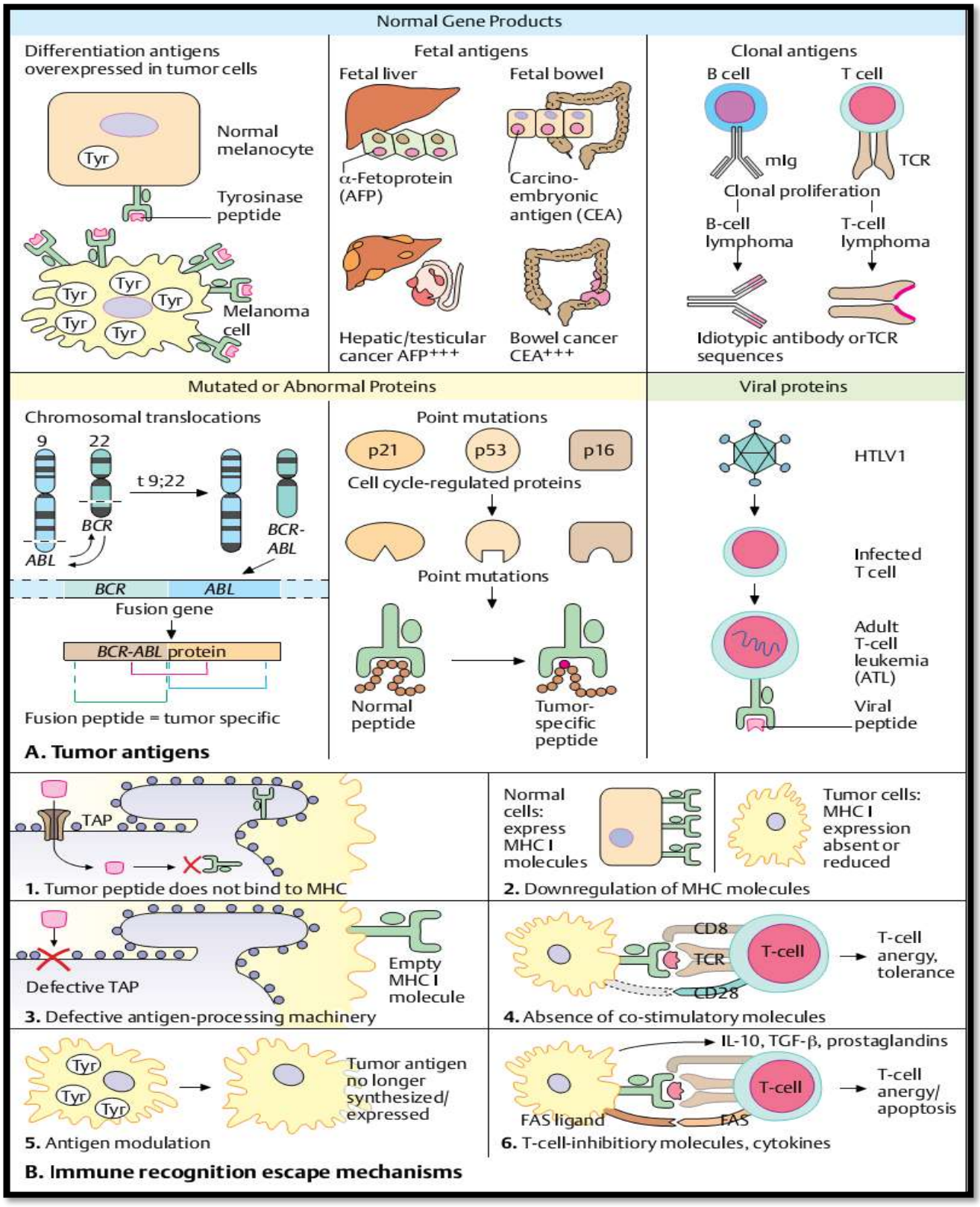
Normal Gene Products
Differentiation antigens overexpressed in tumor cells
Tyr
Normal melanocyte
Tyrosinase peptide
Melanoma cell
Fetal antigens
Fetal liver
Fetal bowel
α-Fetoprotein (AFP)
Carcino-embryonic antigen (CEA)
Hepatic/testicular cancer AFP+++
Bowel cancer CEA+++
Clonal antigens
B cell
T cell
mIg
TCR
Clonal proliferation
B-cell lymphoma
T-cell lymphoma
Idiotypic antibody or TCR sequences
Mutated or Abnormal Proteins
Chromosomal translocations
9
22
t 9;22
BCR
ABL
BCR-ABL
Fusion gene
BCR-ABL protein
Fusion peptide = tumor specific
Point mutations
p21
p53
p16
Cell cycle-regulated proteins
Point mutations
Normal peptide
Tumor-specific peptide
Viral proteins
HTLV1
Infected T cell
Adult T-cell leukemia (ATL)
Viral peptide
A. Tumor antigens
TAP
1. Tumor peptide does not bind to MHC
Normal cells: express MHC I molecules
Tumor cells: MHC I expression absent or reduced
2. Downregulation of MHC molecules
Defective TAP
Empty MHC I molecule
3. Defective antigen-processing machinery
CD8
TCR
T-cell
CD28
T-cell anergy, tolerance
4. Absence of co-stimulatory molecules
Tumor antigen no longer synthesized/ expressed
5. Antigen modulation
IL-10, TGF-β, prostaglandins
T-cell
FAS ligand
FAS
T-cell anergy/ apoptosis
6. T-cell-inhibitory molecules, cytokines
B. Immune recognition escape mechanisms

Lecture No. 29-30

Transplantation

Transplantation is the process of taking cells, tissues, or organs, called **a graft**, from one individual and placing them into a different individual.A graft transplanted between two genetically different individuals of the same species is called an **allogeneic graft (or allograft)**.

Transplantation of tissues from one individual to a genetically nonidentical recipient leads to a specific immune response called **rejection** that can destroy the graft. The antigens recognised during rejection are referred to as **alloantigens**. The key alloantigens are those encoded by the MHC. In humans these are known as **HLA** molecules is to present peptide antigen to a complementary T cell receptor.

Allogeneic MHC molecules may be presented on donor APCs to recipient T cells (**direct allorecognition**), or the alloantigens may be picked up by host APCs that enter the graft or reside in draining lymphoid organs and be processed and presented to T cells as peptides associated with self MHC molecules (**indirect allorecognition**).

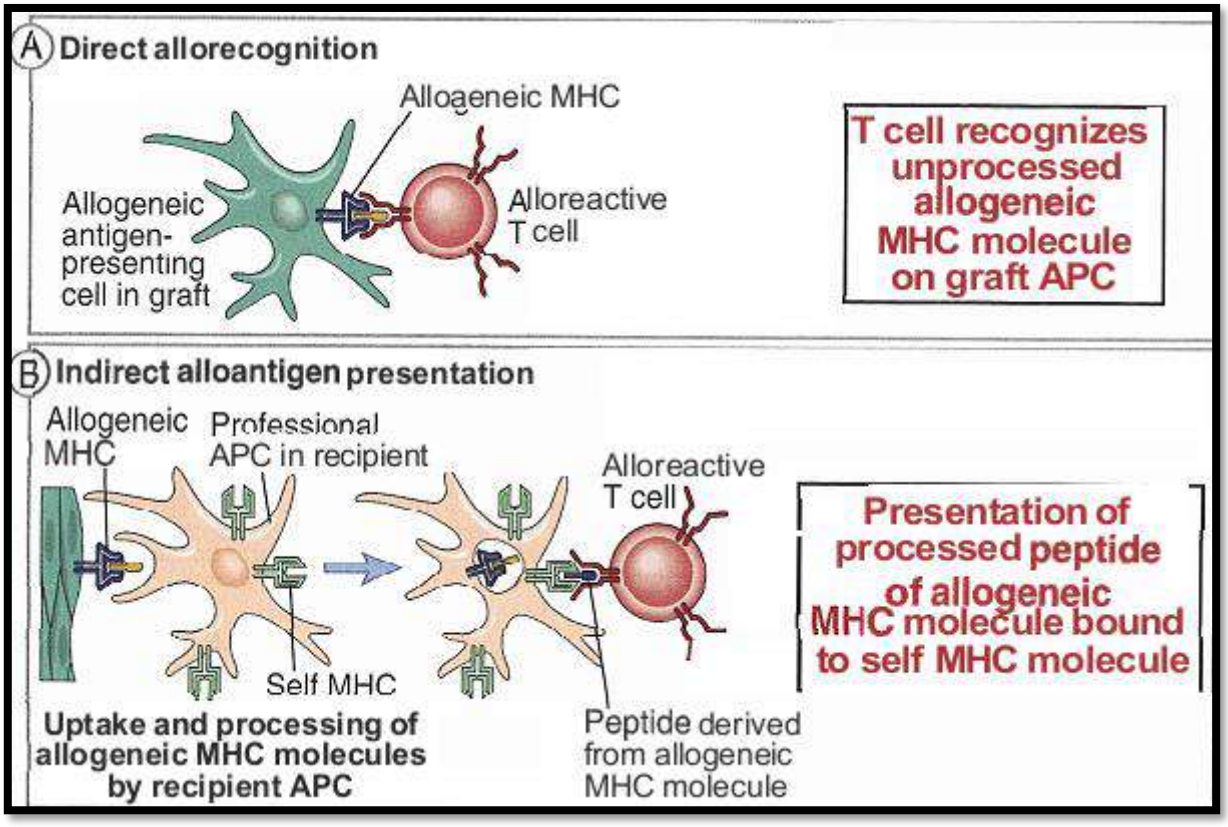

Figure: Direct and indirect alloantigen recognition.

Types of transplant

- **Autograft or autologous transplant:** the organ/tissue is transplanted within the same individual. It does not undergo rejection.
- **Syngraft or syngeneic transplant:** the organ/tissue is transplanted between genetically identical subjects, such as monozygotic twins or inbred laboratory animals. It does not undergo rejection.
- **Allograft or allogeneic transplant:** the organ/tissue is transplanted between genetically non-identical members of the same species. It is rejectes unless immunosuppression is instituted.
- **Xenograft or xenogeneic transplant:** the organ/tissue is transplanted between members of the different species. It is rejected hyperacutely.

Classification of rejection

Rejection can be classified according to the timescale of its appearance and to the immune mechanism involved (see Table.1)**.**

Table.1 Classification of rejection

Type	Time after transplantation	Probable mechanism
Hyperacute	Minutes	Preformed antibodies
Accelerated acute	1-5 days	T lympocytes
Acute	From 2nd	T lympocytes
Chronic	Months or years	Antibodies, complement, adhesion molecules

In classical immune responses, it is the balance between the different components of the immune system that decrees the magnitude and manifestation of the rejection process. Once a naïve helper CD4 cell designated to T_H0 has recognized as alloantigen, presented by a professional antigen-presenting cell such as a dendritic cell, which is singularly competent in providing the co-stimulation signals needed to arouse naïve cells, it can become either a T_H1 or a T_H2 cell according to the microenvironment it encounters and the nature of the alloantigenic stimulus. If the surrounding medium is rich in IL-12 a macrophage-derived cytokines, the naïve T_H0 CD4 cell will commit itself to the T_H1 phenotype and function and orchestrate the activation of CD8 cytotoxic T cells and of macrophage through the release of IL-2 and IFN-γ. If ,however, the prevailing cytokine is IL-4, the naïve CD4 cell will differentiate into the T_H2 phenotype, and though the secretion of IL-4 and IL-10 will direct the activation of B lympocytes and antibody production.

Graft-versus-host reaction

Immunocomponent cells from thegraft recognise alloantigens of the recipient and the recipient develops a disorder known as **the graft-versus-host (GVH) reaction**. This reaction is common after transplantation of **bone marrow**, even when the matching between donor and recipient has been stringent. When GVH becomes symptomatic the term **graft-versus-host disease (GVHD)** is more appropriate. GVHD has been described not only following bone marrow transplantation but also, occasionally, after **liver transplantation** and even after **blood transfusions**. GVHD can be divided into two distinct entities: **acute disease**, occuring in the first 1 or 2 months after transplantation, and **chronic disease**, developing at least 2 or 3 months after transplantation.

In humans, GVHD typically affects **the skin, liver, intestinal tract and immune system** and appears within days or weeks after bone marrow transplantation. In **mild GVH** reactions, patients manifest erythema of the palms, soles and ears. Hepatic signs of mild reactions are limited to asymptomatic hyperbilirubinaemia, and gastrointestinal involvement is indicated by mild diarrhoea, in the case of **sever GVHD**, the skin lesions can include a necrolytic disorder, characterized by blister formation and desquamation. Severe liver abnormalities include jaundice, elevation of alkaline phosphatase, which denotes cholestasis, and of transaminase, a sign of liver cell damage. Sever gastrointestinal GVHD includes abdominal pain and diarrhea, with life-threating electrolyte abnormalities. These manifestations are the result of injury to the epithelial cells of the target organs. Mild GVH may resolve spontaneously or with mild immunosuppressive treatments. Sever GVH is usually unresponsive to treatments and has a fatal outcomes.